

REMARKS

Claims 1, 3-5, 7-13, 27, 28, 30, 32-34 and 51 are currently under examination in the application. Claims 35-50 and 55-80 are withdrawn. Claims 1 and 51 are amended. Claims 2 and 52 are cancelled herein without prejudice. No new matter is added.

The only outstanding issue with regard to the allowance of the claims is one of alleged indefiniteness under 35 U.S.C. §112, second paragraph with regard to the “detecting” step recited in each of independent claims 1 and 51. The Examiner argues that the recited detection of a “change in a signal” as proposed in the amendment filed in response to the Final Office Action is vague because the addition of detector molecule itself results in a change in signal. However, the Examiner indicated that a requirement for the immobilization of either the one or more tagged binding partner polypeptides recited in (i) or the one or more binding partner polypeptides that bind to said one or more tagged binding partner polypeptides recited in (ii) would overcome the indefiniteness issue. Applicants have amended claims 1 and 51 herein to recite “wherein said one or more tagged binding partner polypeptides or said one or more binding partner polypeptides are immobilized on a solid support” as originally recited in dependent claims 2 and 52. The amendment adds no new matter.

Applicants have also amended the recitation of “said binding” in line 1 of clause B of claim 1 to refer to “binding of said one or more tagged binding partner polypeptides of (i) to said one or more binding partner polypeptides of (ii),” in order to more clearly recite the claimed invention. The amendment adds no new matter.

In view of the above, Applicants submit that the claims as amended herein are definite under 35 U.S.C. §112, second paragraph. Applicants respectfully request reconsideration of the claims.

Date: July 5, 2005

Respectfully submitted,



Name: Mark J. FitzGerald

Registration No.: 45,928

Customer No.: 29933

Palmer & Dodge LLP

111 Huntington Avenue

Boston, MA 02199-7613

Tel: 617-239-0100

COPY



Atty. Docket No.: 10069/1062

PATENT

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Application of: Roger Craig
Serial No.: 09/770,102
Filed: January 25, 2001
Entitled: Compositions and Methods for
Monitoring the Modification of
Modification Dependent Binding
Partner Polypeptides

Examiner: Counts, G.

Group Art Unit: 1641

Conf. No.: 5353

CERTIFICATE OF MAILING UNDER 37 C.F.R. § 1.8a

I hereby certify that this correspondence (and any paper or fee referred to as being enclosed) is being deposited with the United States Post Office as First Class Mail on the date indicated below in an envelope addressed to Mail Stop AF, Commissioner for Patents, P.O. Box 1450, Alexandria, VA 22313-1450.

Mary Wilson

Name of Person Mailing Paper

Signature of Person Mailing Paper

Mail Stop AF
Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

TRANSMITTAL LETTER

Enclosed for filing in the above-identified patent application, please find the following documents:

1. Response to Final Office Action mailed January 5, 2005; and
2. Return Post Card.

The Commissioner for Patents is hereby authorized to charge any fees to Deposit Account No. 16-0085, Reference 10069/1062. A duplicate of this transmittal letter is enclosed for this purpose.

Respectfully submitted,

Date: March 3, 2005

Name: Mark J. FitzGerald

Registration No.: 45,928

Customer No.: 29933

Palmer & Dodge LLP

111 Huntington Avenue

Boston, MA 02199-7613

Tel: 617-239-0100

Decoded

Response Due

Statutory Period

Palmer & Dodge LLP
Patent Department



Atty. Docket No.: 10069/1062 PATENT
IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Application of: Roger Craig
Serial No.: 09/770,102
Filed: January 25, 2001
Entitled: Compositions and Methods for
Monitoring the Modification of
Modification Dependent Binding
Partner Polypeptides

Examiner: Counts, G.

Group Art Unit: 1641

Conf. No.: 5353

CERTIFICATE OF MAILING UNDER 37 C.F.R. § 1.8a

I hereby certify that this correspondence (and any paper or fee referred to as being enclosed) is being deposited with the United States Post Office as First Class Mail on the date indicated below in an envelope addressed to Mail Stop AF, Commissioner for Patents, P.O. Box 1450, Alexandria, VA 22313-1450.

Mary Wilson

Name of Person Mailing Paper

Signature of Person Mailing Paper

Mail Stop AF
Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

AMENDMENT UNDER 37 C.F.R. §1.116

Sir:

This Amendment is being filed in response to the Final Office Action mailed from the U.S. Patent and Trademark Office on January 5, 2005 in the above-identified application. Reconsideration and further examination are requested.

Amendments to the Claims are shown in the "Listing of the Claims" which begins on page 2 of this paper.

Remarks begin on page 17 of this paper.

Please enter the following amendments and remarks.

The following Listing of the Claims will replace all prior versions and all prior listings of the claims in the present application:

Listing of the Claims:

1. (Currently Amended) A method for monitoring activity of one or more enzymes comprising the steps of:
 - A. mixing:
 - (i) one or more tagged binding partner polypeptides;
 - (ii) one or more binding partner polypeptides that bind to said one or more tagged binding partner polypeptides of (i); and
 - (iii) one or more enzymes that add or remove a moiety to or from said one or more binding partner polypeptides or one or more tagged binding partner polypeptides;wherein said one or more tagged binding partner polypeptides or said one or more binding partner polypeptides comprise one or more sites for the addition or removal of said moiety, wherein addition or removal of said moiety promotes binding of said one or more binding partner polypeptides with the corresponding one or more tagged binding partner polypeptides; under conditions which promote binding of said one or more binding partner polypeptides with said one or more tagged binding partners; and
 - B. detecting said binding, wherein the step of detecting binding comprises adding one or more detector molecules comprising a first region that associates with a tag of a said one or more tagged binding partner ~~polypeptide~~ polypeptides and a second region comprising one or more reporter molecules, wherein said binding is evidenced by a change in a signal generated by said reporter molecule, and wherein detection of binding as a result of said mixing is indicative of enzyme activity.
2. (Previously Presented) The method of claim 1 wherein said one or more tagged binding partner polypeptides or said one or more binding partner polypeptides are immobilized on a solid support.

3. (Previously Presented) The method of claim 1 wherein both said one or more tagged binding partner polypeptides and said one or more binding partner polypeptides comprise one or more sites for the addition or removal of a moiety.
4. (Previously Presented) The method of claim 1 wherein said one or more tagged binding partner polypeptides are tagged with one or more fluorescent molecules.
5. (Original) The method of claim 4 wherein said detecting comprises monitoring the rate of diffusion of said fluorescent molecule.
6. (Cancelled)
7. (Previously Presented) The method of claim 1 wherein said one or more detector molecules comprise a said first region selected from the group consisting of a coiled-coil, an antigen, an epitope, an antibody, a single chain antibody, an oligonucleotide, avidin and its analogues and derivatives, and streptavidin, its analogs and derivatives; and wherein said one or more detector molecules comprise a said second region selected from the group consisting of an enzyme, a radioisotope, a radionuclide, a fluorochrome, and a fluorescent protein.
8. (Previously Presented) The method of claim 1 wherein one or more detector molecules are pre-bound to the one or more tagged binding partner polypeptides.
9. (Previously Presented) The method of claim 1 wherein the tag on said one or more tagged binding partner polypeptides comprises one or more radioactive molecules.
10. (Original) The method of claim 9 wherein said detecting comprises monitoring the presence or absence of radioactivity.
11. (Previously Presented) The method of claim 1 wherein said one or more binding partner polypeptides of step (ii) are tagged.
12. (Original) The method of claim 11 wherein the tag on said one or more binding partner polypeptides of step (ii) and said one or more tagged binding partner polypeptides comprises one or more fluorescent molecules.
13. (Original) The method of claim 12 wherein said detecting comprises monitoring the presence or absence of fluorescent resonance energy transfer (FRET).
14. (Cancelled)
15. (Cancelled)
16. (Cancelled)

17. (Cancelled)
18. (Cancelled)
19. (Cancelled)
20. (Cancelled)
21. (Cancelled)
22. (Cancelled)
23. (Cancelled)
24. (Cancelled)
25. (Cancelled)
26. (Cancelled)
27. (Previously Presented) The method of claim 1 wherein said one or more sites comprise a sequence which directs modification by an enzyme selected from the group consisting of a kinase, a phosphatase, a UDP-N-acetylglucosamine-dolichyl-phosphate-N-acetylglucosamine phosphotransferase, an O-GlcNAc transferase, a glycylopeptide-N-tetradecanoyl transferase, a carbohydrate transferase, a ubiquitin activating enzyme E1, a ubiquitin conjugating enzyme E2, a ubiquitin conjugating enzyme Ubc9, a ubiquitin protein ligase E3, a poly (ADP-ribose) polymerase, a fatty acyl transferase, and an NAD:Arginine ADP ribosyltransferase.
28. (Previously Presented) The method of claim 1 wherein said site promotes addition of a chemical moiety selected from the group consisting of a phosphate moiety (PO₄), a ubiquitin moiety, a glycosyl moiety, an ADP-ribosyl moiety, a fatty acid moiety, and a sentrin moiety.
29. (Cancelled)
30. (Previously Presented) The method of claim 1 wherein said site promotes removal of a chemical moiety selected from the group consisting of a phosphate moiety (PO₄), a ubiquitin moiety, a glycosyl moiety, an ADP-ribosyl moiety, a fatty acid moiety, and a sentrin moiety.
31. (Cancelled)
32. (Previously Presented) The method of claim 1 wherein said tag on said one or more tagged binding partner polypeptides is selected from the group consisting of a coiled-coil,

an antigen, an epitope, an antibody, a single chain antibody, a nucleic acid binding domain, a radioactive amino acid, a fluorescent molecule, a reporter enzyme, and biotin.

33. (Previously Presented) The method of claim 1 wherein said site is recombinant.

34. (Previously Presented) The method of claim 1 wherein said site is naturally occurring.

35. (Withdrawn) A kit comprising:

one or more tagged binding partner polypeptides;

one or more binding partner polypeptides that correspond to said one or more tagged binding partner polypeptides of step (I); and

packaging materials;

wherein said one or more tagged binding partner polypeptides or said one or more binding partner polypeptides comprise one or more sites for the addition or removal of a moiety, wherein addition or removal of said moiety promotes binding of said one or more binding partner polypeptides with the corresponding one or more tagged binding partner polypeptides; and wherein said one or more polypeptides and said one or more tagged binding partner polypeptides bind in a manner dependent on modification of said site.

36. (Withdrawn) The kit of claim 35 wherein said one or more tagged binding partner polypeptides or said one or more binding partner polypeptides are immobilized on a solid support.

37. (Withdrawn) The kit of claim 35 further comprising one or more detector molecules comprising a first region that associates with said one or more tagged binding partner polypeptides and a second region comprising one or more reporter molecules.

38. (Withdrawn) The kit of claim 35 wherein said one or more binding partner polypeptides further comprise one or more tags.

39. (Withdrawn) A kit comprising:

one or more tagged binding partner polypeptides;

one or more binding partner polypeptides; and

packaging materials;

wherein said one or more tagged binding partner polypeptides or said one or more binding partner polypeptides comprise one or more sites for the addition or removal of a moiety, wherein addition or removal of said moiety promotes dissociation of said one or more binding partner polypeptides from the corresponding tagged binding partner

- polypeptides, wherein said one or more polypeptides and said one or more tagged binding partner polypeptides dissociate in a manner dependent on modification of said site.
40. (Withdrawn) The kit of claim 39 wherein said one or more tagged binding partner polypeptides or said one or more binding partner polypeptides are immobilized on a solid support.
41. (Withdrawn) The kit of claim 39 further comprising one or more detector molecules comprising a first region that associates with said one or more tagged binding partner polypeptides and a second region comprising one or more reporter molecules.
42. (Withdrawn) The kit of claim 39 wherein said one or more binding partner polypeptides further comprise one or more tags.
43. (Withdrawn) A composition comprising:
- one or more tagged binding partner polypeptides;
 - one or more binding partner polypeptides that correspond to said one or more tagged binding partner polypeptides of step (I); and
 - packaging materials;
- wherein said one or more tagged binding partner polypeptides or said one or more binding partner polypeptides comprise one or more sites for the addition or removal of a moiety, wherein addition or removal of said moiety promotes binding of said one or more binding partner polypeptides with the corresponding one or more tagged binding partner polypeptides; wherein said one or more binding partner polypeptides and said one or more tagged binding partner polypeptides bind in a manner dependent on modification of said site.
44. (Withdrawn) The composition of claim 43 wherein said one or more tagged binding partner polypeptides or said one or more binding partner polypeptides are immobilized on a solid support.
45. (Withdrawn) The composition of claim 43 further comprising one or more detector molecules comprising a first region that associates with said one or more tagged binding partner polypeptides and a second region comprising one or more reporter molecules.
46. (Withdrawn) The composition of claim 43 wherein said one or more binding partner polypeptides further comprise one or more tags.
47. (Withdrawn) A composition comprising:

one or more tagged binding partner polypeptides;

one or more binding partner polypeptides that correspond to said one or more tagged binding partner polypeptides of step (I); and

packaging materials;

wherein said one or more tagged binding partner polypeptides or said one or more binding partner polypeptides comprise one or more sites for the addition or removal of a moiety, wherein addition or removal of said moiety promotes dissociation of said one or more binding partner polypeptides from the corresponding one or more tagged binding partner polypeptides; wherein said one or more polypeptides and said one or more tagged binding partner polypeptides dissociate in a manner dependent on modification of said site.

48. (Withdrawn) The composition of claim 47 wherein said one or more tagged binding partner polypeptides or said one or more binding partner polypeptides are immobilized on a solid support.

49. (Withdrawn) The composition of claim 47 further comprising one or more detector molecules comprising a first region that associates with said one or more tagged binding partner polypeptides and a second region comprising one or more reporter molecules.

50. (Withdrawn) The composition of claim 47 wherein said one or more binding partner polypeptides further comprise one or more tags.

51. (Currently Amended) A method of screening for a candidate modulator of enzymatic activity comprising:

A. mixing:

- (i) one or more tagged binding partner polypeptides comprising a tag;
- (ii) one or more binding partner polypeptides that bind to said one or more tagged binding partner polypeptides of (i); and
- (iii) one or more enzymes that adds or removes a moiety to or from said binding partner polypeptide or said one or more tagged binding partner polypeptides;

wherein said one or more tagged binding partner polypeptides or said one or more binding partner polypeptides comprise one or more sites for the addition or removal of said moiety, wherein addition or removal of said moiety promotes

binding of said one or more binding partner polypeptides with the corresponding one or more tagged binding partner polypeptides; under conditions which promote binding of said one or more binding partner polypeptides and said one or more tagged binding partner polypeptides; and

- B. detecting binding of said one or more binding partner polypeptides to said one or more tagged binding partner polypeptides in both the presence and absence of a candidate modulator of enzymatic activity, wherein the step of detecting binding comprises adding one or more detector molecules ~~that are not substrates of said one or more enzymes and comprise~~ comprising a first region that associates with said tag of said one or more tagged binding partner polypeptides and a second region comprising one or more reporter molecules, wherein said binding is evidenced by a change in a signal generated by said reporter molecule, and wherein detection of the amount binding in the presence of the candidate modulator that is lesser or greater as compared to the amount of binding in the absence of the candidate modulator indicates modulation of enzymatic activity by said candidate modulator.

52. (Previously Presented) The method of claim 51 wherein said one or more tagged binding partner polypeptides or said one or more binding partner polypeptides are immobilized on a solid support.

53. (Cancelled)

54. (Cancelled)

55. (Withdrawn) A method for monitoring activity of one or more protease enzymes comprising the steps of:

mixing:

one or more tagged binding partner polypeptides;

one or more immobilized binding partner polypeptides that correspond to said one

or more tagged binding partner polypeptides of step (1); and

one or more protease enzymes

wherein said one or more tagged binding partner polypeptides or said one or more immobilized binding partner polypeptides is susceptible to protease digestion, wherein said protease digestion promotes binding of said one or more immobilized binding partner polypeptides with the corresponding one or more tagged binding partners; under

conditions which promote binding of said one or more immobilized binding partner polypeptides with said one or more tagged binding partners; and detecting said binding, wherein detection of binding as a result of said mixing is indicative of protease activity.

56. (Withdrawn) A method for monitoring activity of one or more protease enzymes comprising the steps of:
mixing:

one or more tagged binding partner polypeptides;
one or more immobilized binding partner polypeptides that correspond to said one or more tagged binding partner polypeptides of step (i); and
one or more protease enzymes

wherein said one or more tagged binding partner polypeptides or said one or more immobilized binding partner polypeptides is susceptible to protease digestion, wherein said protease digestion promotes dissociation of said one or more immobilized binding partner polypeptides from the corresponding one or more tagged binding partners; under conditions which promote dissociation of said one or more immobilized binding partner polypeptides from said one or more tagged binding partners; and detecting said dissociation, wherein detection of dissociation as a result of said mixing is indicative of protease activity.

57. (Withdrawn) The method of claim 55 or 56 wherein the tag on said one or more tagged binding partner polypeptides comprises one or more fluorescent molecules.
58. (Withdrawn) The method of claim 57 wherein said detecting comprises monitoring the rate of diffusion of said fluorescent molecule.
59. (Withdrawn) The method of claim 55 or 56 wherein the step of detecting binding further comprises adding one or more detector molecules comprising a first region that associates with said one or more tagged binding partner polypeptides and a second region comprising one or more reporter molecules.
60. (Withdrawn) The method of claim 59 wherein said one or more detector molecules comprise a said first region selected from the group consisting of a coiled-coil, an antigen, an antibody, an oligonucleotide, a single chain antibody, avidin and its analogues and derivatives, and streptavidin, its analogs and derivatives; and wherein said one or

more detector molecules comprise a said second region selected from the group consisting of an enzyme, a radioisotope, a radionuclide, a fluorochrome, and a fluorescent protein.

61. (Withdrawn) The method of claim 55 or 56 wherein one or more detector molecules are pre-bound to said one or more tagged binding partner polypeptides.
62. (Withdrawn) The method of claim 55 or 56 wherein the tag on said one or more tagged binding partner polypeptides comprises one or more radioactive molecules.
63. (Withdrawn) The method of claim 62 wherein said detecting comprises monitoring the presence or absence of radioactivity.
64. (Withdrawn) The method of claim 55 or 56 wherein said one or more immobilized binding partner polypeptides are tagged.
65. (Withdrawn) The method of claim 64 wherein said one or more immobilized binding partner polypeptides comprises a tag, and the tag on said one or more immobilized binding partner polypeptides and said one or more tagged binding partner polypeptides comprises one or more fluorescent molecules.
66. (Withdrawn) The method of claim 65 wherein said detecting comprises monitoring the presence or absence of fluorescent resonance energy transfer (FRET).
67. (Withdrawn) A kit comprising:
 - one or more tagged binding partner polypeptides;
 - one or more immobilized binding partner polypeptides that correspond to said one or more tagged binding partner polypeptides of step (i); and
 - packaging materials;
 - wherein said one or more tagged binding partner polypeptides or said one or more immobilized binding partner polypeptides is susceptible to protease digestion, wherein said protease digestion promotes binding of said one or more immobilized binding partner polypeptides with the corresponding one or more tagged binding partners; under conditions which promotes binding of said one or more immobilized binding partner polypeptides with said one or more tagged binding partners.
68. (Withdrawn) A kit comprising:
 - one or more tagged binding partner polypeptides;

one or more immobilized binding partner polypeptides that correspond to said one or more tagged binding partner polypeptides of step (i); and

packaging materials;

wherein said one or more tagged binding partner polypeptides or said one or more immobilized binding partner polypeptides is susceptible to protease digestion, wherein said protease digestion promotes dissociation of said one or more immobilized binding partner polypeptides from the corresponding one or more tagged binding partners; under conditions which promote dissociation of said one or more immobilized binding partner polypeptides from said one or more tagged binding partners.

69. (Withdrawn) The kit of claim 67 or 68 further comprising one or more detector molecules comprising a first region that associates with said one or more tagged binding partner polypeptides and a second region comprising one or more reporter molecules.
70. (Withdrawn) The kit of claim 67 or 68 wherein the one or more immobilized binding partner polypeptides further comprise one or more tags.
71. (Withdrawn) A composition comprising:
one or more tagged binding partner polypeptides;
one or more immobilized binding partner polypeptides that correspond to said one or more tagged binding partner polypeptides of step (i); and
packaging materials;
wherein said one or more tagged binding partner polypeptides or said one or more immobilized binding partner polypeptides is susceptible to protease digestion, wherein said protease digestion promotes binding of said one or more immobilized binding partner polypeptides with the corresponding one or more tagged binding partners; under conditions which promotes binding of said one or more immobilized binding partner polypeptides with said one or more tagged binding partners.
72. (Withdrawn) A composition comprising:
one or more tagged binding partner polypeptides;
one or more immobilized binding partner polypeptides that correspond to said one or more tagged binding partner polypeptides of step (i); and
packaging materials;

wherein said one or more tagged binding partner polypeptides or said one or more immobilized binding partner polypeptides is susceptible to protease digestion, wherein said protease digestion promotes dissociation of said one or more immobilized binding partner polypeptides from the corresponding one or more tagged binding partners; under conditions which promote dissociation of said one or more immobilized binding partner polypeptides from said one or more tagged binding partners.

73. (Withdrawn) The composition of claim 71 or 72 further comprising one or more detector molecules comprising a first region that associates with said one or more tagged binding partner polypeptides and a second region comprising one or more reporter molecules.

74. (Withdrawn) The composition of claim 71 or 72 wherein said one or more immobilized binding partner polypeptides further comprise one or more tags.

75. (Withdrawn) A method of screening for a candidate modulator of enzymatic activity comprising:

mixing:

one or more tagged binding partner polypeptides;

one or more immobilized binding partner polypeptides that correspond to said one or more tagged binding partner polypeptides of step (i); and

one or more protease enzymes

wherein said one or more tagged binding partner polypeptides or said one or more immobilized binding partner polypeptides is susceptible to protease digestion, wherein said protease digestion promotes binding of said one or more immobilized binding partner polypeptides to the corresponding one or more tagged binding partners; under conditions which promote binding of said one or more immobilized binding partner polypeptides to said one or more tagged binding partners; and

detecting binding of said one or more immobilized binding partner polypeptides to said one or more tagged binding partner polypeptides in both the presence and absence of a candidate modulator of protease activity, wherein detection of the amount binding in the presence of the candidate modulator that is lesser or greater as compared to the amount of binding in the absence of the candidate modulator indicates modulation of protease activity by said candidate modulator.

76. (Withdrawn) A method of screening for a candidate modulator of enzymatic activity comprising:
mixing:
one or more tagged binding partner polypeptides;
one or more immobilized binding partner polypeptides that correspond to said one or more tagged binding partner polypeptides of step (i); and
one or more protease enzymes
wherein said one or more tagged binding partner polypeptides or said one or more immobilized binding partner polypeptides is susceptible to protease digestion, wherein said protease digestion promote dissociation of said one or more immobilized binding partner polypeptides from the corresponding one or more tagged binding partners; under conditions which promotes dissociation of said one or more immobilized binding partner polypeptides from said one or more tagged binding partners; and
detecting dissociation of said one or more immobilized binding partner polypeptides from said one or more tagged binding partner polypeptides in both the presence and absence of a candidate modulator of protease activity, wherein detection of the amount dissociation in the presence of the candidate modulator that is lesser or greater as compared to the amount of dissociation in the absence of the candidate modulator indicates modulation of protease activity by said candidate modulator.
77. (Withdrawn) A method for monitoring activity of one or more enzymes comprising the steps of:
A. mixing:
(i) one or more tagged binding partner polypeptides;
(ii) one or more binding partner polypeptides that correspond to said one or more tagged binding partner polypeptides of (i), wherein said tagged binding partner of (i) and said one or more binding partner polypeptides that correspond to said one or more tagged binding partner polypeptides associate; and
(iii) one or more enzymes that add or remove a moiety to or from said one or more binding partner polypeptides or one or more tagged binding partner

polypeptides; wherein said one or more tagged binding partner polypeptides or said one or more binding partner polypeptides comprise one or more sites for the addition or removal of said moiety, wherein addition or removal of said moiety promotes dissociation of said one or more binding partner polypeptides from the corresponding one or more tagged binding partner polypeptides; under conditions which promote dissociation of said one or more binding partner polypeptides from said one or more tagged binding partners; and

- B. detecting said dissociation, wherein the step of detecting dissociation comprises adding one or more detector molecules comprising a first region that associates with said one or more tagged binding partner polypeptides and a second region comprising one or more reporter molecules, wherein detection of dissociation as a result of said mixing is indicative of enzyme activity.

78. (Withdrawn) A method of screening for a candidate modulator of enzymatic activity comprising:

A. mixing:

- (i) one or more tagged binding partner polypeptides;
- (ii) one or more binding partner polypeptides that correspond to said one or more tagged binding partner polypeptides of (i), wherein said tagged binding partner of (i) and said one or more binding partner polypeptides that correspond to said one or more tagged binding partner polypeptides associate; and
- (iii) one or more enzymes that adds or removes a moiety to or from said binding partner polypeptide or said one or more tagged binding partner polypeptides; wherein said one or more tagged binding partner polypeptides or said one or more binding partner polypeptides comprise one or more sites for the addition or removal of said moiety, wherein addition or removal of said moiety promotes dissociation of said one or more binding partner polypeptides from the corresponding one or more tagged binding partner polypeptides; under conditions which promote dissociation of said one or more binding partner polypeptides and said one or more tagged binding partner polypeptides; and

- B. detecting dissociation of said one or more binding partner polypeptides ~~to~~ from said one or more tagged binding partner polypeptides in both the presence and absence of a candidate modulator of enzymatic activity, wherein the step of detecting dissociation comprises adding one or more detector molecules comprising a first region that associates with said one or more tagged binding partner polypeptides and a second region comprising one or more reporter molecules, wherein detection of the amount of dissociation in the presence of the candidate modulator that is lesser or greater as compared to the amount of dissociation in the absence of the candidate modulator indicates modulation of enzymatic activity by said candidate modulator.
79. (Withdrawn) A method for monitoring activity of one or more enzymes comprising the steps of:
- A. mixing:
- (i) one or more tagged binding partner polypeptides;
 - (ii) one or more binding partner polypeptides that correspond to said one or more tagged binding partner polypeptides of (i), wherein said tagged binding partner of (i) and said one or more binding partner polypeptides that correspond to said one or more tagged binding partner polypeptides associate; and
 - (iii) one or more enzymes that add or remove a moiety to or from said one or more binding partner polypeptides or one or more tagged binding partner polypeptides; wherein said one or more tagged binding partner polypeptides or said one or more binding partner polypeptides comprise one or more sites for the addition or removal of said moiety, wherein addition or removal of said moiety promotes association of said one or more binding partner polypeptides from the corresponding one or more tagged binding partner polypeptides; under conditions which promote association of said one or more binding partner polypeptides from said one or more tagged binding partners; and
- B. detecting said association, wherein the step of detecting association comprises adding one or more detector molecules comprising a first region that associates with said one or more tagged binding partner polypeptides and a second region comprising one or

more reporter molecules, wherein detection of association as a result of said mixing is indicative of enzyme activity.

80. (Withdrawn) A method of screening for a candidate modulator of enzymatic activity comprising:

A. mixing:

- (i) one or more tagged binding partner polypeptides;
- (ii) one or more binding partner polypeptides that correspond to said one or more tagged binding partner polypeptides of (i), wherein said tagged binding partner of (i) and said one or more binding partner polypeptides that correspond to said one or more tagged binding partner polypeptides associate; and
- (iii) one or more enzymes that adds or removes a moiety to or from said binding partner polypeptide or said one or more tagged binding partner polypeptides;

wherein said one or more tagged binding partner polypeptides or said one or more binding partner polypeptides comprise one or more sites for the addition or removal of said moiety, wherein addition or removal of said moiety promotes association of said one or more binding partner polypeptides from the corresponding one or more tagged binding partner polypeptides; under conditions which promote association of said one or more binding partner polypeptides and said one or more tagged binding partner polypeptides; and

B. detecting association of said one or more binding partner polypeptides ~~to~~ from said one or more tagged binding partner polypeptides in both the presence and absence of a candidate modulator of enzymatic activity, wherein the step of detecting association comprises adding one or more detector molecules comprising a first region that associates with said one or more tagged binding partner polypeptides and a second region comprising one or more reporter molecules, wherein detection of the amount of association in the presence of the candidate modulator that is lesser or greater as compared to the amount of association in the absence of the candidate modulator indicates modulation of enzymatic activity by said candidate modulator.

REMARKS

At the outset, Applicants wish to thank Examiners Counts and Le for the telephone interview conducted by Applicant's representatives Mark FitzGerald and Barbara Gyure on February 11, 2005. During the interview, all pending claims were discussed, with particular emphasis on independent claims 1 and 51. More particularly, the rejection under 35 U.S.C. §112, second paragraph regarding the detection of positive signal from the detector molecule regardless of binding between the tagged binding partner polypeptide and the binding partner polypeptide was discussed. The Examiner agreed that the specification provides support for assays in which a detector molecule that may give a signal even when the binding partners are unbound would work to provide a meaningful result. The Examiner agreed to consider the clarifying amendments proposed herein.

Claims 1-5, 7-13, 27, 28, 30, 32-34, 51 and 52 are currently under examination in the application. Claims 35-50 and 55-80 are withdrawn. Claims 1 and 51 are proposed to be amended. The amendments find support in the specification and are discussed in the relevant sections below. No new matter is added.

Claim Objection:

The Office Action objects to Claim 1, stating that the recitation in part (B) "of a said tagged binding partner polypeptide" should be "of said tagged binding partner polypeptides." Applicants have amended the language herein to recite "of said one or more tagged binding partner polypeptides." Support for the language of the amendment is found, for example, at page 9, lines 7-9. Applicants submit that the proposed amendment is sufficient to overcome the objection and respectfully request that it be withdrawn.

Rejection under 35 U.S.C. §112, Second Paragraph:

The Office Action rejects claims 1-5, 7-13, 27, 28, 30, 32-34, 51 and 52 as vague and indefinite under 35 U.S.C. §112, second paragraph, stating

"The detector molecule as recited binds to the tagged binding partner and regardless if the tagged binding partner binds to the binding partner polypeptide or not the detector molecule will bind to the tagged binding partner and thus a

positive signal will always be detected. Claims 1 and 51 as instantly recited will not work.”

As discussed in the interview, Applicants submit that the specification recites a number of assay formats in which a meaningful result can be obtained using a detector molecule as recited, even where the detector molecule may have a detectable signal when the binding partners are not bound to each other. The possibility that the recited detector molecule may give a detectable signal when associated with the tag of the tagged binding partner polypeptide independent of the binding of the tagged binding partner to a binding partner polypeptide is not relevant where the binding is evidenced by a *change* in a signal generated by the reporter molecule.

For example, the specification describes the use of Fluorescence Correlation Spectroscopy (FCS) at page 75, line 3 to page 76, line 2. As noted in the specification, FCS measures the motion of diffusion of a tagged molecule. The specification states:

In FCS, a focused laser beam illuminates a very small volume of solution, on the order of 10-15 liter, which at any given point in time contains only one molecule of the many under analysis. The diffusion of single molecules through the illuminated volume, over time, results in bursts of fluorescent light as the labels of the molecules are excited by the laser. Each individual burst, resulting from a single molecule, can be registered.

A labeled polypeptide will diffuse at a slower rate if it is large than if it is small. Thus, multimerized polypeptides will display slow diffusion rates, resulting in a lower number of fluorescent bursts in any given time frame, while labeled polypeptides which are not multimerized or which have dissociated from a multimer will diffuse more rapidly. Binding of polypeptides according to the invention can be calculated directly from the diffusion rates through the illuminated volume. (page 75, lines 9-19; emphasis added)

Thus, even where the fluorescent tag gives a detectable signal independent of the binding status of the binding partners under investigation, when FCS is used for detection, that signal will *change* or be altered in a manner that is dependent upon the binding status of the partners.

As another example, assays in which FRET is used to detect binding (described in the specification at numerous places, e.g., page 9, line 19 to page 10, line 2, page 21, line 17 to page 22, line 3, to name but two) are functional in the instance where one or both members of the fluorescent donor/acceptor pair are detectable regardless of binding status. Here again, the

detected signal *changes* in a manner dependent upon the binding status of the binding partner polypeptides.

As another example, the specification describes the use of Fluorescence Polarization (FP), which measures changes in the rotation of a fluorescently tagged molecule. The specification states at page 76, line 11 to page 77, line 2:

Fluorescently labeled binding partner polypeptides emit light in the same polarized plane when excited with plane polarized light if the molecule remains stationary throughout the excited state. However, the excited molecule can rotate or tumble out of the plane of polarized light during the excited state and emit light in a different plane. Emission light intensity can be monitored in more than one plane. *The degree to which emission intensity moves from one plane to another plane is related to the mobility of the fluorescently labeled binding partner polypeptide. Where a fluorescently labeled binding partner polypeptide is bound to its corresponding binding partner, it will move very little during the excited state interval because it is a large molecule, and the emitted light will remain highly polarized with respect to the excitation plane. If a fluorescently labeled binding partner is not bound to its corresponding binding partner it will rotate or tumble faster because it is a small molecule. The resulting emitted light will be depolarized relative to the excitation plane.* (Emphasis added)

Thus, when using FP for detection, even though a detector molecule may give a signal when binding partner polypeptides are bound or unbound, the change in the size of the complex upon binding will yield a *change* in the signal detected. Applicants submit that the same is true when, for example, fluorescence anisotropy, which also measures the rotation of fluorescent molecules (see page 76, lines 3-8), is used.

In view of the above, Applicants submit that the invention as claimed in independent claims 1 and 51 will work. As discussed during the interview, and simply to remove any doubt, Applicants propose herein to amend each of claims 1 and 51 to recite "wherein said binding is evidenced by a change in a signal generated by said reporter molecule." Applicants note that such a change includes, for example, a change in the diffusion rate of a labeled molecule or complex, a change in the rotational rate of a labeled molecule or complex, a change in emission spectrum of a fluorescent label, as well as, for example, a change in the location of signal from a label, e.g., when a labeled molecule in solution binds to an immobilized binding partner. In view of the above and the proposed amendment, Applicants submit that the invention as claimed in the

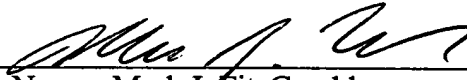
amended claims will work, and respectfully request that the rejection under §112, second paragraph be withdrawn.

Applicants also wish to point out one additional amendment proposed to clarify that which is claimed. In claim 51, part (B), Applicants propose to remove the language "that are not substrates of said one or more enzymes." Applicants submit that this language was mistakenly included as an amendment in the "Listing of the Claims" provided in the Office Action response filed October 26, 2004. The Examiner will note that the language was not discussed in the "Remarks" section of that response, and that the claim as proposed to be amended herein (i.e., without that language) remains novel and non-obvious over the cited references, in part due to the failing of each of the cited references to teach or suggest a detector molecule that "associates with a tag of said tagged binding partner polypeptides" as required by the claim. The amendment adds no new matter.

In view of the above, Applicants submit that all issues raised in the Final Office Action have been addressed herein. Applicants respectfully request entry of the amendments and reconsideration of the claims.

Respectfully submitted,

Date: March 3, 2005



Name: Mark J. FitzGerald
Registration No.: 45,928
Customer No.: 29933
Palmer & Dodge LLP
111 Huntington Avenue
Boston, MA 02199-7613
Tel: 617-239-0100